

REMARKS

Claims 1-34 are pending in this application. Claims 1, 4 and 6 have been amended. Claim 5 has been cancelled without prejudice or disclaimer of the subject matter therein. Claims 9-34 have been withdrawn as being a non-elected subject matter.

Claim 1 has been amended to incorporate the limitation of claim 5. Claim 4 has been amended to delete some of fluorescent dyes listed the group and the term "derivatives thereof" for each compound in the group. Claim 6 has been amended to revise the term "said primer" to "primer." Amended claim 1 recites "A fluorescent probe for real-time detection of amplification of nucleic acid, wherein a fluorescent dye of which intensity of fluorescence is varied when the dye is intercalated into a double-stranded nucleic acid, replaces at least a base of an oligonucleotide of which base sequence is complementary with at least a part of said nucleic acid." Support for these amendments can be found throughout the specification and the claims as originally filed, for example, original claim 5 and Table 1.

Claim 5 has been cancelled in accordance with the amendment of claim 1.

In addition, the abstract has been amended to correctly read "931 C to 96 C" as "93°C to 96°C", "50 C to 571 C" as "50°C to 57°C", "701 C to 74°C" as "70°C to 74°C", "931 C to 961 C" as "93°C to 96°C" and "501 C to 57 C" as "50°C to 57°C."

The amendments to and cancellation of claims are solely for advancing prosecution. Applicants, by amending or cancelling any claims herein, make no

admission as to the validity of any rejection made by the Examiner against any of these claims. Applicants reserve the right to reassert the original claim scope of any claim amended herein, in a continuing application.

No new matter has been introduced to this application within the meaning of 35 U.S.C. §132.

In view of the following, further and favorable consideration is respectfully requested.

- I. At pages 4 of the Official Action, claim 4 has been rejected under 35 USC §112, 1st paragraph as failing to comply with the written description requirement and the enablement requirement.***

The Examiner indicates that "All of the current claims encompass a genus of fluorescent dyes which are different from the ones disclosed in the specification or known in the prior art. While the fluorescent dyes such as acridine, acridine orange, actinomycin, etc. are known in the art, Applicants have not described a single derivative of any of the claimed 19 fluorescent dyes. Therefore the genus includes variants for which no written description is provided in the specification. This large genus is represented in the specification by only 19 fluorescent dyes known in the art. Thus, ***Applicants has express possession of only 19 fluorescent dyes***, in a genus which comprise hundreds of millions of different possibilities. ... " (Emphasis added).

In addition, the Examiner indicates that the term "derivative" used with respect to all of the claimed fluorescent dyes critical or essential to the practice of the

invention, but not included in the claim(s) is not enabled by the disclosure.

In this regard, Applicants submit that claim 4, as amended, fully comply with the written description and enablement requirements of 35 USC § 112, first paragraph.

The test under 35 U.S.C. 112, first paragraph, for determining compliance with the written description requirement is whether the application clearly conveys that an applicant has invented the subject matter which is claimed. *In re Barker*, 194 USPQ 470, 473 (CCPA 1977); MPEP 2163. Also, the applicant must convey to the public what the applicant claims as the invention so that the public may ascertain if the patent applicant claims anything in common use or already known. MPEP § 2163. Lastly, the specification must convey that the applicant was in possession of the invention. MPEP § 2163. The Examiner is respectfully reminded that the Examiner has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. *In re Wertheim*, 191USPQ 90, 98 (CCPA 1976).

The enablement provision of the Patent Act requires that the patentee provide a written description of the invention "in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same." 35 U.S.C. § 112, first paragraph (2000). The purpose of this requirement is to ensure that "the public knowledge is enriched by the patent specification to a degree at least commensurate with the

scope of the claims.” *Nat’l Recovery Techs., Inc. v. Magnetic Separation Sys., Inc.*, 166 F.3d 1190, 1195-96 (Fed. Cir. 1999); see_also Donald S. Chisum, 3 *Chisum on Patents* § 7.01 (2002).

Accordingly, the specification must provide sufficient teaching such that one skilled in the art could make and use the full scope of the invention without undue experimentation. *CFMT, Inc. v. Yieldup Int’l Corp.*, 349 F.3d 1333, 1338 (Fed. Cir. 2003); *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997); *In re Wands*, 858 F.2d 731, 736-37 (Fed. Cir. 1988). “The key word is ‘undue,’ not experimentation.” *Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). Routine experimentation does not constitute undue experimentation. See *Johns Hopkins University v. Cellpro, Inc.*, 152 F.3d 1342 (Fed. Cir. 1998). That is, the specification need only teach those aspects of the invention that one skilled in the art could not figure out without undue experimentation. See, e.g., *Nat’l Recovery Techs.*, 166 F.3d at 1196 (“The scope of enablement . . . is that which is disclosed in the specification plus the scope of what would be known to one of ordinary skill in the art without undue experimentation.”); *Wands*, 858 F.2d at 736-37 (“Enablement is not precluded by the necessity for some experimentation such as routine screening.”). “Nothing more than objective enablement is required, and therefore it is irrelevant whether this teaching is provided through broad terminology or illustrative examples.” See *In re Wright*, 999 F.2d 1557 (Fed. Cir. 1993).

Although the ultimate determination of whether one skilled in the art could make and use the claimed invention without undue experimentation is a legal one, it is based on underlying findings of fact. *CFMT*, 349 F.3d at 1337. Furthermore, “[w]hether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations.” *Wands*, 858 F.2d at 737.

Some of these considerations, commonly referred to as “the *Wands* factors,” include “(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.” *Id.*; see also *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1213 (Fed. Cir. 1991) (stating that the *Wands* factors “are illustrative, not mandatory” and that what is relevant to an enablement determination depends upon the facts of the particular case).

In the present application, amended claim 4 recites only fourteen (14) specific compounds, by deleting the terms “the derivatives thereof” for each of the fourteen (14) compounds, and Cy-dyes derivatives, for the fluorescent dyes. For the fourteen (14) specific compounds for the fluorescent dyes, the Examiner has conceded in the Official Action as meeting the written description requirement.

Regarding the “Cy-dyes derivatives,” Applicants draw the Examiner’s

attention that the preparation of a specific derivative of Cy-dyes is well described in Example 2 of the present specification. See pages 20 and 21 of the corresponding PCT publication in this regard. Example 2 titles "Synthesis of DNA Green Phosphoramidite" and describes the preparation of a phosphoramidite containing fluorescent material as shown by chemical formula 1 therein. Example 2 further describes that the phosphoramidite containing fluorescent material is represented as DNA GREEN phosphoramidite, and this is a derivative of Cy-dyes.

Accordingly, the present specification clearly conveys that at the time of the invention Applicants had a possession of the subject matter of claim 4 even respect to the Cy-dyes derivatives.

In addition, in view of Example 2 discussed above, it is also clear that the specification provide sufficient teaching and guidelines such that one skilled in the art could make and use the full scope of the invention without undue experimentation. Other Wands factors also favor the enablement of claim 4.

Accordingly, Applicants submit that claim 4, as amended, complies with the written description requirement as well as the enablement requirement under 35 USC §112, 1st paragraph.

Therefore, reconsideration and withdrawal of these rejections are respectfully requested.

- II. At page 7 of the Official Action, claim 6 has been rejected under 35 USC §112, 2nd paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter, due to the term "said primer".**

Applicants submit that claim 6 as amended does not contain the term "said primer," which according to the Examiner has no antecedent basis. Instead, claim 6 has the term "primer" and it is easily conceived by a person of ordinary skill in the art that primer is necessary for amplification of nucleic acid.

Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

- III. At page 7 of the Official Action, claims 1-7 have been rejected under 35 USC §102(b) as being anticipated by Mergny et al. (Nucl. Acids Res., vol. 22, pp. 920-928, 1994) as evidenced by Morgan et al. (Nucl. Acids Res., vol. 7, pp. 547-569, 1979)**

The Examiner indicates that claims 1-7 are anticipated by Mergny et al. since Mergny et al. teach an oligonucleotide probe with a fluorescent dye, such as ethidium bromide, attached to it (page 921, 6th paragraph; Fig. 1). Further, the Examiner indicates that it is evidenced by Morgan et al. that fluorescence of ethidium bromide increases with it is bound to double-stranded DNA.

Applicants respectfully traverse this rejection. The test for anticipation is whether each and every element as set forth is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987); MPEP §2131. The identical invention must be shown in as complete detail as is contained in the claim. *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989); MPEP

§2131. The elements must also be arranged as required by the claim. *In re Bond*, 15 USPQ2d 1566 (Fed. Cir. 1990).

In the present application, claim 1 recites "A fluorescent probe for real-time detection of amplification of nucleic acid, wherein a fluorescent dye of which intensity of fluorescence is varied when the dye is intercalated into a double-stranded nucleic acid, **replaces at least a base of an oligonucleotide** of which base sequence is complementary with at least a part of said nucleic acid." Claims 2-4, 6 and 7 are directly dependent from claim 1, and thus contain all the limitations of claim 1.

Mergny et al. describes oligonucleotides covalently linked to a fluorescent dye. The fluorescent dye in the probe of Mergny et al., however, is connected to oligonucleotide, and in this regard the fluorescent dye should be **connected either at 3' or at 5' end of the oligonucleotide** for a Fluorescence Energy Transfer. In contrast, in the present claims, the fluorescent dye replaces a base of an oligonucleotide and thus it may **replace a base at 3' end, 5' end and/or in the middle region of the oligonucleotide**. See Table 1 in the present specification. Accordingly, Mergny et al. teach a fluorescent probe having a different structure from the claimed probe.

Further, this structural difference is supported by the specific usage of the present claims, i.e., real-time detection of amplification of nucleic acid. Also, the structural difference between the present claims and Mergny et al. results in difference in the fluorescence detection method as well. Mergny et al. mandatorily

need two probes such as a probe of 3'-terminus donor fluorescence dye and a probe of 5'-terminus acceptor fluorescence dye because they make use of the phenomena so called "FRET (Fluorescence Resonance Energy Transfer)", phenomena where lights emitted by shorter wavelength dye (energy donor) induces an excitation of longer wavelength dye (energy acceptor). In contrast, the present claims, without such limitation, accomplish its intended object with only one probe.

In view of foregoing, Mergny et al. fail to teach each and every element of the present claims, as required by *Verdegaal Bros. v. Union Oil Co. of California*.

Morgan et al., which is cited by the Examiner as evidencing that the fluorescence of ethidium bromide increases when it is bound to double stranded DNA, do not remedy the deficiencies of Mergny et al. Nowhere does the Morgan et al. reference describe the replacement of fluorescent dyes to a base of oligonucleotide.

Accordingly, Applicants submit that Mergny et al. do not anticipate present claims 1-7.

Reconsideration and withdrawal is therefore respectfully requested.

CONCLUSION

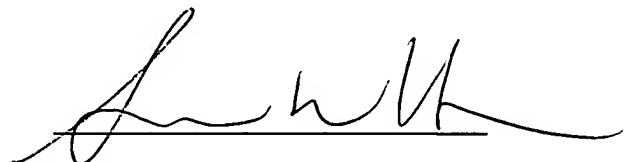
In view of the foregoing, applicants submit that the pending claims are in condition for allowance. Early notice to this effect is earnestly solicited. The Examiner is invited to contact the undersigned attorney if it is believed such contact will expedite the prosecution of the application.

If the Examiner has any questions or comments regarding this matter, he is welcomed to contact the undersigned attorney at the below-listed number and address.

In the event this paper is not timely filed, applicants petition for an appropriate extension of time. Please charge any fee deficiency or credit any overpayment to Deposit Account No. 14-0112.

Respectfully submitted,

THE NATH LAW GROUP

A handwritten signature in black ink, appearing to read 'G. Nath', is written over a horizontal line.

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